COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

I
We RHONE-POULENC SANTE of,
"Les Miroirs",
18 Avenue d'Alsace,
F-92400, Courbevoie,
FRANCE.

LODGED AT SUB-OFFICE
- 7 MAY 1986
Melbourne

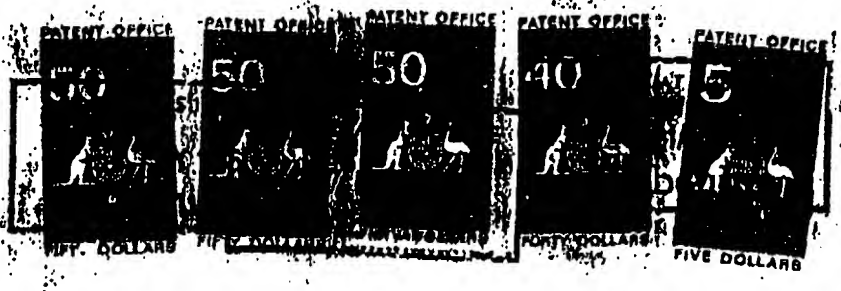
hereby apply for the grant of a Standard Patent for an invention entitled:

"COMPOSITIONS FOR THE PREPARATION OF MICROPARTICLES PERMITTING A PROLONGED RELEASE OF A BIOLOGICALLY ACTIVE SUBSTANCE"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

| Number | Convention Country | Date |
|---|---|---|
| 85 07013 | FRANCE | 9 May, 1985 |




The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 6th day of May 19 86

K. W. Rimington

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

To: THE COMMISSIONER OF PATENTS

Davies & Collison, Melbourne and Canberra.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

# DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention entitled: "COMPOSITIONS FOR THE PREPARATION OF MICROPARTICLES PERMITTING A PROLONGED RELEASE OF A BIOLOGICALLY ACTIVE SUBSTANCE"

Insert title of invention.

I/We Jacques PILARD, Executiv of Rhone-Poulenc Sant

Authorised to sign on behalf of Rhone-Poulenc Sante of, "Les Miroirs", 18 Avenue d'Alsace, F-92400, Courbevoie, FRANCE.

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

LODGED AT SUB-OFFICE
- 7 MAY 1986
Melbourne

do solemnly and sincerely declare as follows :-

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert nam. of applicant company.

1. (a) ~~I am the actual inventor or one of the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows :-~~

or (b) I am authorized by RHONE-POULENC SANTE, a French Body Corporate of "Les Miroirs", 18 Avenue d'Alsace, F 92400 COURBEVOIE, FRANCE

the applicant..... for the patent to make this declaration on ~~his~~ their behalf.

Cross out which-ever of paragraphs 2(a) or 2(b) does not apply

(a) relates to application made by inventor(s)
(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventor(s).

2. (a) ~~I am the actual inventor or one of the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows :-~~

or (b)

Jehan-Yves Drouin, of 4 rue du Mérou, 92290 Chatenay-Malabry, France.

Michel Veillard, of 12 Rue du Docteur Roux, 92330 Sceaux, France

Both french citizens

~~I~~ are the actual inventors..... of the invention and the facts upon which the applicants..... ~~is~~ are entitled to make the application are as follows :-

State manner in which applicant(s) derive title from inventor(s)

Employment Contract, therefore the applicant would, if a patent were granted upon an application made by the inventors, be entitled to have the patent assigned to it.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ~~was~~ made

in .....FRANCE..... on the ... 9th May 1985 .....

by RHONE POULENC SANTE .....

..... on the .....

by.....

in ..... on the .....

by.....

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~ the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Courbevoie this 21st day of April 1986

Signature of declarant(s) (no attestation required)

.....

BY J. PILARD
RHONE POULENC SANTE

Note. Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) AUSTRALIAN PATENT ABSTRACT
(19) AU
(11) AU-A-57224/86

(54) EXTRUDED PROLONGED RELEASE PHARMACEUTICALS

(71) RHONE-POULENC SANTE

(21) 57224/86 (22) 7.5.86 (24) 9.5.85
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(72) JEHAN-YVES DROUIN AND MICHEL VEILLARD
(74) DM

(57) Claim

It has now been found, and this is the subject of the present invention, that microparticles permitting a prolonged release of a biologically active substance may be obtained directly by extrusion, without coating and/or spheronisation, of a composition comprising the active substance, one or more compatible polymers, and one or more lipid excipients and, if appropriate, adjuvants which are usually employed in galenic pharmacy such as antistatic agents, wetting agents or diluents.

1. A composition for the preparation by extrusion of microparticles permitting a prolonged release of a biologically active substance, which composition comprises a biologically active substance, one or more compatible polymers, and from 10 to 40% by weight of the composition of a lipid excipient which either is a mixture of two or more lipid excipients one of which dissolves or gels the polymer or polymers and another of which has lubricating properties

.../2



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or has both the property of dissolving or gelling the polymer or polymers and lubricating properties.

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COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE:
57224/86

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
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Priority:

Related Art:

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Name of Applicant: RHONE-POULENC SANTE

Address of Applicant: "Les Miroirs",
18 avenue d'Alsace,
92400 Courbevoie,
France

Actual Inventor(s): JEHAN-YVES DROUIN and MICHEL VEILLARD

Address for Service: Davies & Collison,
Patent Attorneys,
1 Little Collins Street,
Melbourne,
Victoria 3000

Complete Specification for the invention entitled:

"COMPOSITIONS FOR THE PREPARATION OF MICROPARTICLES PERMITTING A PROLONGED RELEASE OF A BIOLOGICALLY ACTIVE SUBSTANCE"

The following statement is a full description of this invention, including the best method of performing it known to us:-

DESCRIPTION

The present invention relates to the preparation of microparticles which permit a prolonged release of a biologically active substance.

There are in existence various methods for preparing microgranules which permit a prolonged release of an active substance. For example, one method consists in performing the following steps in succession: production of a sucrose-starch seed, impregnation or swelling of the seed with the active substance in the form of powder or solution, and then coating with solutions of polymers which provide the required kinetics of release of the active substance. Another method involves the performance of the following steps in succession: extrusion of a wet mixture containing the active substance, spheronisation of the extrudate, and then coating of the microsphere produced with solutions of polymers which provide the kinetics of release of the active substance. However, these methods are time-consuming and costly.

Furthermore, it often happens that, especially during extrusion, particles of a small size are produced, which have a large area to volume ratio, and this leads to a relatively rapid release of the active substance. To slow down the rate of release, a coating can be applied, after a preliminary spheronisation, in order to obtain a film-forming membrane of known thickness.

It has now been found, and this is the subject of the present invention, that microparticles permitting a prolonged release of a biologically active substance may be obtained directly by extrusion, without coating and/or spheronisation, of a composition comprising the active substance, one or more compatible polymers, and one or more lipid excipients and, if appropriate, adjuvants which are usually employed in galenic pharmacy such as antistatic agents, wetting agents or diluents.

The lipid excipient or excipients must dissolve or gel the polymer and have a lubricating capacity which permits the extrusion. These functions may be performed separately by different excipients or by a single excipient.

The polymers employed to produce the microparticles may be chosen from cellulose ethers (such as ethyl celluloses of the G, K, N and T series, and especially those of the N series, Hercules ), the polymers of acrylic and methacrylic acid esters (such as Eudragit RSPM, RLPM, L and S, and especially RSPM, Röhmpharma ), the copolymers of vinylpyrrolidone and vinyl acetate (such as Kollidon VA 64, B.A.S.F. ), polyvinyl alcohols such as Mowiols (Hoechst ), and vinyl acetate homopolymers such as, for example, Rhodopas BB 3 (Rhône-Poulenc ).

The polymer or polymers is, or are, chosen to take account of the affinity of the active substance for aqueous media. Thus, as a general rule, in the case of a hydrophilic

active substance, bearing in mind the small siz of the microparticles and their large area to volume ratio, it is particularly advantageous to use a non-hydrophilic and nonerodible polymer (such as N-type ethyl cellulose) to obtain a prolonged release over more than 8 hours in man, following oral administration. On the other hand, it is particularly advantageous to use an erodible polymer, that is to say a polymer which can slowly dissolve in water and/or can be digested gradually by the enzymes present in biological liquids, (eg. a copolymer of vinylpyrrolidone and vinyl acetate, such as Kollidon VA 64, BASF), to obtain a complete release of the active substance in 24 hours.

The use of 2 or more polymers forms an additional means for controlling the kinetics of release as a function of the specific characteristics of the active substance. It may also be advantageous, in some cases, to control the kinetics of release by adding to the composition especially hydrophobic polymers, such as polysiloxanes.

The lipid excipients may be chosen from fatty alcohols (cetyl alcohol), fatty acids (stearic acid), esters of $C_{24}$-$C_{36}$ alcohols with fatty acids which may contain 36 carbon atoms (white wax), polycondensates of ethylene oxide with vegetable oils (Cremophors, BASF ; Labrafils, Gattefosse ), hydrogenated vegetable oils (Cutina H.R., Henkel), fatty acid mono-, di- or triglycerides (Compritol 888 or Precirol, Gattefosse ; Imwitor 900 or Softisan 154,

Dynamit Nobel ), and lecithins, and their mixtures.

It is especially advantageous to produce a composition containing a lipid excipient whose melting point is in the region of 50°C, to dissolve or gel the polymer, combined with a second lipid excipient with a higher melting point to promote the lubrication.

A single lipid excipient may be used, such as glycerol palmitostearate (Precirol, Gattefosse ), when the latter combines a relatively low melting point with appropriate lubricating properties and has the property of dissolving or gelling the polymer.

The lipid excipient content in the extrudable compositions according to the present invention represents between 10 and 40% by weight of the composition and it is especially advantageous to use a mixture of lipid excipients, in which the lubricating excipient represents from 60 to 80% by weight of the mixture of lipid excipients.

The biologically active substance in the extrudable compositions according to the present invention generally represents from 5 to 40% by weight of the composition.

The rate of release of the active substance is influenced by the size of the microparticles, the nature and the quantity of lipid excipient and the affinity of the active substance for the lipid excipient.

In general, the rate of release of the active substance increases when the size of the microparticles diminishes, since this decrease in size is accompanied by an increase in the area to volume ratio.

The rate of release is a function of the comparative affinity of the active substance for, on the one hand, the lipid excipients forming the microparticles and, on the other hand, for the aqueous media into which the active substance is released, and it is also a function of the rate of diffusion of the active substance in the matrix, which is related to the nature and the quantity of the polymer or polymers. Consequently, a lipophilic active substance, such as ketoprofen, will diffuse less rapidly in a lipid excipient for which the active substance has a higher affinity. Conversely, a less lipophilic active substance, such as riodipine or acebutolol hydrochloride, will diffuse more rapidly in a lipid excipient for which the active substance has less affinity.

To produce the microparticles according to the invention, it is preferable to use a lipid excipient or a mixture of lipid excipients in which the polymer acting as the structuring agent is soluble or partly soluble.

The microparticles may be produced by an extrusion process which comprises extruding a homogeneous granulate consisting of a mixture of one or more polymers and of one or more lipid excipients containing the active substance through

calibrated orifices.

The granulation may be carried out in a conventional granulator by using the molten lipid excipient or excipients as a wetting liquid, or in an apparatus with a heating jacket, equipped with a rotary knife and a doctor blade, by raising the temperature gradually until the lipid excipients start to melt in order to give rise to the granulation. By using this method it is possible to obtain a granulate whose homogeneity is much greater than when a conventional granulator is employed.

Depending on the texture of the granulate produced, it may be necessary to carry out a size-standardizing operation, before the extrusion, with the aim of breaking up the agglomerates.

The extrusion may be advantageously carried out in an apparatus consisting essentially of two rolls rotating in opposite directions, one being solid and the other being perforated. The granulate, entrained between the two rolls at a high pressure is extruded through the perforated roll in the form of small cylinders of substantially identical diameters, and whose length is virtually constant because of a knife which slices off the extrudate as it leaves the perforations. The extrudates obtained in this manner may be screened, to maintain a product of homogeneous size.

Extrusion of the granulate is made possible because of the temperature rise which takes place between

calibrated orifices.

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Extrusion of the granulate is made possible because of the temperature rise which takes place between

the two rolls. This temperature rise results in partial melting of the lipid excipient which has the l west melting point and which partly dissolves the polymer to give rise to a plastic mass which is extruded and which immediately resolidifies.

It is therefore especially important to control the extrusion temperature. This control may advantageously be carried out by modifying the rate of feed of granulate and/or the speed of rotation of the rolls so that the heat energy is wholly absorbed by the granulate entering between the two rolls.

As a result of this, if the heat input is too low, for example because of an excessively low speed of rotation of the rolls, the extrusion will be only partial and a high proportion of the granulate will need to be recycled, while, if the heat input is too high, for example because of an excessively high speed of rotation of the rolls, the excess heat cannot be absorbed by the granulate before the extrusion, and this leads to a temperature rise causing more extensive melting of the lipid excipient and consequently blocking, thus making the extrusion increasingly difficult.

It is especially advantageous to perform the extrusion through orifices whose diameter is in the region of 1.5 mm.

The microparticles obtained by extrusion of the compositions of the invention are generally in

the form of small cylindrical rods whose length is between 1 and 5 mm and whose diameter is between 1 and 1.5 mm.

The microparticles according to the present invention may be, for example, distributed uniformly in gelatin capsules. Depending on the type of gelatin capsules used, the microparticles may, if appropriate, be subjected to a standardization treatment in order to make their shape and their size compatible with a uniform filling.

It is also possible to fill the gelatin capsules with a mixture of microparticles whose kinetics of dissolving are different.

The following Examples show how the invention may be used in practice.

EXAMPLE 1

Ketoprofen (10 g) is added to molten cetyl alcohol (34 g) at a temperature of 65°C.

The solution thus produced is added in small portions to ethyl cellulose N4 (56 g) placed in a planetary mixer of the "Bouvard" type. The rate of stirring is 50 revolutions/minute. Stirring is continued for 10 minutes until a homogeneous granulate is obtained.

The granulate thus produced is extruded in an Alexander Werk extruder in which the orifices of the perforated roll are 1 mm in diameter.

This produces microgranules which are in the form of small rods whose diameter is between 1 and 1.25 mm and whose length is between 1 and 5 mm.

EXAMPLES 2 to 8

The method of Example 1 is followed, with cetyl alcohol replaced by various lipid excipients.

The results obtained are collated in Table 1.

TABLE 1

| Examples | Lipid excipients | Characteristics |
|---|---|---|
| 2 | Stearic acid | Small rods whose diameter is between 1 and 1.25 mm and whose length is between 1 and 5 mm |
| 3 | White wax | |
| 4 | Imwitor 900 | |
| 5 | Cutina HR | |
| 6 | Precirol | |
| 7 | Compritol 8-88 | |
| 8 | Softisan 154 | |

EXAMPLES 9 to 17

The method of Example 1 is followed, but the nature and the proportions of the lipid excipients and of the polymers are varied; the content of the active substance (ketoprofen) being 10% of the total weight of the composition.

The results obtained are collated in Table 2.

TABLE 2

| Examples | Lipid excipients % | Polymer % | Characteristics |
|---|---|---|---|
| 9 | Cetyl alcohol 15 | Ethyl cellulose N4 75 | Small rods whose diameter is between 1 and 1.25 mm and whose length is between 1 and 5 mm |
| 10 | Cetyl alcohol 10 | Ethyl cellulose N4 80 | |
| 11 | Precirol 34 | Ethyl cellulose N4 56 | |
| 12 | Precirol 15 | Ethyl cellulose N4 75 | |
| 13 | Precirol 10 | Ethyl cellulose N4 80 | |
| 14 | Precirol 34 | Mowiol 4-88 56 | |
| 15 | Precirol 34 | Kollidon VA 64 56 | |
| 16 | Precirol 34 | Rhodopas BB 3 56 | |
| 17 | Precirol 34 | Eudragit RSPM 56 | |

The release of the active substance as a function of time is determined as follows:

The tests are carried out in a standard USP XX dissolution test. The apparatus consists of a water bath controlled at 37°C and containing 6 reactors.

Each reactor is filled with 750 cc of a medium whose pH is equal to 7.4 and which has the following composition:

| | |
|---|---|
| disodium phosphate | 1,302 g |
| citric acid | 40 g |
| distilled water q.s. | 20 litres |

A stirrer rotating at a speed of 120 revolutions/minute is immersed in each reactor.

One gelatin capsule containing 200 mg of microparticles is placed in each reactor at time t = 0.

A 5-cc sample is taken after 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours and 23 hours. The quantity of active substance released is determined in each sample. In the case of ketoprofen, the determination is carried out by means of spectrophotometry at 260 nm.

The results obtained are collated in Table 3.

TABLE 3

| Examples | % of active substance released after | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 min | 1 h | 2 h | 3 h | 4 h | 5 h | 6 h | 23 h |
| 1 | 34 | 40 | 51 | | 61 | | 66 | 83 |
| 2 | 23 | 28 | 37 | 45 | 47 | 52 | | 76 |
| 3 | 12 | 22 | 38 | 47 | 50 | 54 | | 75 |
| 4 | 25 | 38 | | 60 | | | 76 | 92 |
| 5 | 2 | 3 | | 5 | | | 6 | 11 |
| 6 | 5 | 10 | | 30 | | | 45 | 68 |
| 7 | 3 | 4 | 6 | 11 | | 15 | | 44 |
| 8 | 3 | 5 | 6 | 8 | 9 | 10 | | 18 |
| 9 | 19 | 26 | 36 | | 48 | | 53 | 81 |
| 10 | 18 | 24 | 33 | | 43 | | 51 | 76 |
| 11 | 5 | 10 | | 30 | | | 45 | 68 |
| 12 | 4 | 8 | 17 | | 35 | | 47 | 81 |
| 13 | 4 | 8 | 15 | | 26 | | 33 | 60 |
| 14 | 36 | 70 | | 97 | | 98 | | 100 |
| 15 | 26 | 63 | | 90 | | 92 | | 96 |
| 16 | 14 | 36 | 58 | 71 | 75 | | 79 | 85 |
| 17 | 8 | 16 | | 32 | 36 | 40 | | 77 |

EXAMPLE 18

Riodipine (60 g), vinylpyrrolidon -vinyl acetate copolymer (Kollidon VA 64; 165 g), cetyl alcohol (18.75 g) and Precirol (56.25 g) are introduced into the jacketed vessel of an "Olza" granulator which has a doctor blade and a rotating knife at the bottom of the vessel. The temperature of the stirred mixture is gradually raised by circulating hot water at a controlled constant temperature of 65°C in the jacket. A granulate is formed, which is drained off and then extruded in an "Alexanderwerk" extruder.

This produces microparticles which are in the form of small rods whose diameter is in the region of 1.5 mm and whose length is between 1 and 5 mm.

EXAMPLES 19 to 30

The method of Example 18 is followed, but using extrudable mixtures whose composition is given in Table 4.

TABLE 4

| Example No. | Active principle % | Polymer % | Lipid excipient % |
|---|---|---|---|
| 19 | Ketoprofen 20 | Kollidon VA 64 55 | Cetyl alcohol 6.25<br>Precirol 18.75 |
| 20 | Riodipine 20 | Kollidon VA 64 65 | Cetyl alcohol 3.75<br>Precirol 11.25 |
| 21 | Riodipine 20 | Kollidon VA 64 50 | Cetyl alcohol 7.5<br>Precirol 22.5 |
| 22 | Riodipine 20 | Kollidon VA 64 55 | Cetyl alcohol 6.25<br>Cutina HR 18.75 |
| 23 | Riodipine 20 | Kollidon VA 64 55 | Cetyl alcohol 6.25<br>Compritol 888 18.75 |
| 24 | Ketoprofen 20 | Mowiol 4-88 55 | Cetyl alcohol 6.25<br>Precirol 18.75 |
| 25 | Ketoprofen 20 | Rhodopas BB 3 55 | Cetyl alcohol 6.25<br>Precirol 18.75 |
| 26 | Ketoprofen 20 | Kollidon VA 64 54<br>Ethyl cellulose N4 1 | Cetyl alcohol 6.25<br>Precirol 18.75 |
| 27 | Ketoprofen 20 | Kollidon VA 64 45<br>Ethyl cellulose N4 10 | Cetyl alcohol 6.25<br>Precirol 18.75 |
| 28 | Ketoprofen 20 | Kollidon VA 64 25<br>Ethyl cellulose N4 30 | Cetyl alcohol 6.25<br>Precirol 18.75 |

TABLE 4 (continued)

| Example No. | Active principle % | Polymer % | Lipid excipient % |
|---|---|---|---|
| 29 | Ketoprofen 20 | Kollidon VA 64 45<br>Natrosol 250 HHX 10 | Cetyl alcohol 6.25<br>Precirol 18.75 |
| 30 | Riodipine 20 | Kollidon VA 64 45<br>Silicone oil V 300 000 10 | Cetyl alcohol 6.25<br>Precirol 18.75 |

The release of the active substance as a function of time from the microparticles which are the subject of Examples 18 to 30 is determined as follows:

The tests are carried out in a standard USP XX dissolution test. The apparatus consists of a water bath controlled at 37°C, containing 6 reactors.

Each reactor is filled with 1 litre of the dissolving medium which, in the case of riodipine, consists of a 2% solution of Cremophor EL and, in the case of ketoprofen, of an aqueous solution with a pH of 5 and having the following composition:

| | | |
|---|---|---|
| acetic acid | : | 205.9 g |
| disodium phosphate dihydrate | : | 363.12 g |
| demineralized water q.s | : | 20 litres |

A stirrer, which is either a paddle rotating at 100 revolutions/minute or a basket rotating at 120 revolutions/minute, is immersed in each reactor.

The claims defining the invention are as follows:

1. A composition for the preparation by extrusion of microparticles permitting a prolonged release of a biologically active substance, which composition comprises a biologically active substance, one or more compatible polymers, and from 10 to 40% by weight of the composition of a lipid excipient which either is a mixture of two or more lipid excipients one of which dissolves or gels the polymer or polymers and another of which has lubricating properties or has both the property of dissolving or gelling the polymer or polymers and lubricating properties.

2. A composition according to claim 1, wherein the polymer is a cellulose ether, a polymer of an acrylic or methacrylic acid ester, a copolymer of vinylpyrrolidone and vinyl acetate, a polyvinyl alcohol, or a vinyl acetate homopolymer, or a mixture thereof.

3. A composition according to claim 1 or 2, wherein the lipid excipient is a fatty alcohol, fatty acid, an ester of a fatty alcohol with a fatty acid, a hydrogenated vegetable oil, a polycondensate of ethylene oxide with a vegetable oil, a fatty acid mono-, di- or triglyceride, a lecithin, or a mixture thereof.

4. A composition according to claim 1, 2 or 3 wherein the said active substance is 5 to 40% by weight of the composition.

5. A composition according to any of claims 1 to 4 wherein a mixture of lipid excipients is used and the lubricating excipient is 60 to 80% by weight of the said mixture of lipid excipients.

6. A composition according to any of claims 1 to 5 which additionally contains a highly hydrophobic polymer.

7. A composition according to claim 6, wherein the highly hydrophobic polymer is a polysiloxane.

8. A composition according to any of claims 1 to 7 which additionally contains one or more diluents, wetting agents, and/or antistatic agents.

9. A composition according to any one of claims 1 to 8 wherein the biologically active substance is ketoprofen.

10. A composition according to any one of claims 1 to 8 wherein the biologically active substance is nicardipine.

11. A composition according to any one of claims 1 to 8 wherein the biologically active substance is acebutolol hydrochloride.

12. A composition according to claim 1 substantially as described in any one of the foregoing Examples.

13. Microparticles permitting a prolonged release of a biologically active substance which are produced by extrusion of a composition according to any one of claims 1 to 12.

14. A pharmaceutical capsule containing microparticles as claimed in claim 13.

15. Th steps, features, compositions and compounds r f rred to or indicated in the specification and/or claims f this application, individually or c ll ctiv ly, and any and all combinati ns of any two or more of said steps or features.

DATED this 6th day of May, 1986.

RHONE-POULENC SANTE
By its Patent Attorneys
DAVIES & COLLISON